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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,494	06/05/2001	Tseng-hui Timothy Chen	COUL-012/01US	7143

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Cynthia L. Shumate
Corixa Corporation
1125 Columbia Street
Suite 200
Seattle, WA 98104-2048

EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	13

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,494	CHEN ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14-24,28 and 29* is/are rejected.

7)☒ Claim(s) *10-13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-24, 28 and 29 in Paper No. 13 is acknowledged. It is noted that applicant has elected the nucleotide sequence represented as SEQ ID NO: 7, comprising the nucleotide sequence encoding the leader peptide SEQ ID NO: 3, as the specific embodiment of their invention. Applicant is advised that this was an election of distinct inventions, and not an election of species as set forth in the response to the restriction requirement. Current Office practice is to separate distinct nucleotide and/or protein sequences into individual inventions, as was set forth in the restriction requirement. It is further acknowledged that applicant has elected an immunoglobulin or immunoadhesin as set forth in the Markush-type group of claim 4, in response to the restriction requirement.

Claims 1-29 are currently pending in the instant application.

Claims 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claims 1-24, 28 and 29 are ready for examination with regard to the specific sequences SEQ ID NOS: 3 and 7, and with regard to an immunoglobulin or immunoadhesin.

Priority

Applicant's claim for domestic priority to US Application No. 60/209,517 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statement filed August 16, 2002 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 13-24, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Skerra et al. (Science 240:1038-1041, 1998; see entire document; henceforth Skerra).

In order to understand how Skerra is prior art with regard to the rejected claims, it is necessary to point out the limitations of the claims in a pointed manner. To most accurately achieve this goal, the rejection is set forth as follows: 1) the prior art will be explained in a general sense as to how the limitations are anticipated, without details concerning the specific limitations regarding the leader peptide sequences; 2) the limitations of each leader peptide will be addressed with regard to the two leader peptides described in the prior art. As it regards the ompA and phoA leader peptides, these sequences are well known and published, and therefore it is understood that these sequences are disclosed in the reference, although the sequences are not explicitly recited.

Skerra teaches an expression vector for use in the production of the antigen-binding fragment of McPC603 (i.e., an immunoglobulin) in E. coli bacterial cells (see for example the

Abstract, Figures 1 and 2, and page 1039, right side, paragraphs 1-3). The expression vector shown in Figure 1 as pASK22, has the following construction with regard to the claim language: a "first sequence" encoding the ompA leader sequence, operably linked to a "third sequence" which is the coding sequence for the heavy chain for McPC603 (i.e., an immunoglobulin), and a "fourth sequence" encoding the phoA leader peptide sequence, operably linked to a "fifth sequence" which is the coding sequence for the light chain for McPC603 (i.e., an immunoglobulin). The "first" and "third" sequences form a specific fusion protein, as do the "fourth" and "fifth" sequences, wherein the "third" and "fifth" sequences are 3' to the first and fourth sequences, respectively (see for example Figure 1). In this construct, a ribosome-binding site (i.e., the "second sequence" as recited in the claims) must necessarily be present in order to get expression of the fusion proteins because there can be no translation without the binding of a ribosome. Since the fusion proteins are successfully expressed in this construct (see for example Figure 2), the construct must necessarily contain a ribosome-binding site (i.e., the "second sequence" recited in the claims). Significantly, the heavy and light chains of McPC603 are polypeptide subunits of a multimeric protein, thus the recombinant fusion proteins are also part of a multimeric protein. Thus, in general, Skerra anticipates claims 1-9 of the instant specification, as well as claims 28 and 29, which are directed to claims for designing the nucleotides. Furthermore, claims 14-20 are directed to an expression vector comprising the nucleotide sequences as set forth in claims 1-9, with the notable exception that claims 14 and 19 requires the presence of a bacterial promoter. As Skerra teaches such a plasmid, pASK22, which does indeed contain a bacterial promoter (the lac promoter) operably linked to the nucleic acids comprising the anticipated fusion proteins (see for example Figure 1), Skerra also anticipates the

expression vector claims 14-20. Additionally, claims 21-23 are directed to methods for producing and isolating the fusion proteins produced by the expression vectors, specifically in a bacterial cell. Skerra also teaches the production of the fusion proteins using the expression vectors and E. coli bacterial cells (see for example Figure 2). Significantly, the protein that was produced was functional (see for example page 1040, left side, third full paragraph). Thus, without completely addressing the limitations concerning the leader peptides, Skerra teaches all of the general limitations regarding claims 1-9, 14-24, 28 and 29.

Skerra also uses leader peptides which meet the limitations set forth in the claims regarding there being two or more positively charged amino acids at the N-terminus, a region of 7-16 hydrophobic amino acids, a C-terminal region having the amino acid sequence Z-X-Z (wherein A is a "small-chained" amino acid and X is any amino acid), and a "helical disrupter located between the hydrophobic and Z-X-Z sequence. To demonstrate this, it is necessary to recite the sequences of ompA and phoA, located below:

ompA- MKKTAIAIAVALAGFATVAQA

phoA- MKQSTIALALLPLLFTPVTKA

The final residue is indicated as the cleavage site for removal of the leader peptide following secretion. Significantly, the ompA sequence has two K residues, which are positively charged amino acids, both within two residues of the N-terminus. This is followed by a stretch of at least 9 hydrophobic amino acids (AIAIAVALA), a known helix-disrupter (G), and then a Z-X-Z sequence (AQA). As a result ompA meets the limitations of the leader sequence as set

forth in the limitations of the claims. Concerning the phoA sequence, there are also two positively charged amino acids at the N-terminus (K and Q, where Q, having a side-chain pK of ~8.0, carries a positive charge at physiological pH). This is closely followed by a stretch of at least 10 hydrophobic amino acids (IALALLPLLF), a known helix-disrupter (P), and then a Z-X-Z sequence (TKA). As a result, the phoA sequence also meets the limitations set forth in the claims. Upon considering this specific information with regards to the general teachings of Skerra as outlined above, it is clear that Skerra anticipates the invention as claimed in claims 1-9, 14-24, 28 and 29.

Allowable Subject Matter

Claims 10-13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, RemyYucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
July 23, 2003

DAVID GUZO
PRIMARY EXAMINER